

Collateral arteries in pulmonary atresia with ventricular septal defect

A precarious blood supply

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SUMMARY In pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries lung growth and survival depend on the size and continued patency of the collateral arteries. Arterial structure was examined in 13 collaterals, taken from the necropsy specimens of seven children, six of whom died during the first seven months of life. Serial reconstruction was made of two collaterals, from the aorta to the intrapulmonary vessels, and the other collaterals were examined by taking sections at intervals along the same course.

The collateral arteries arose from the aorta either as elastic vessels with a wide lumen or as muscular arteries when they were stenosed. Nearly all vessels rapidly came to resemble muscular systemic arteries, the external and lumen diameter becoming smaller. All collateral arteries save one showed areas of intimal proliferation which varied in the extent to which they surrounded and encroached on the lumen. In addition, four collaterals contained large intimal cushions which severely narrowed or even occluded the lumen. At the anastomosis of collateral and intrapulmonary artery intimal cushions were seen in all collaterals examined and the extent to which the structures reduced lumen diameter varied. The structure of collaterals is compared with that of growing systemic arteries and the ductus arteriosus, emphasis being given to the different types of intimal change. The clinical relevance of these findings is discussed.

The major aortopulmonary collateral arteries found in pulmonary atresia with ventricular septal defect either anastomose with a lobar pulmonary artery, with a segmental intrapulmonary artery or, less commonly, with a central pulmonary artery.¹ The segmental pulmonary arteries which anastomose with collateral arteries have no connection with the sixth arch or its branches within the lung. They do not differ either structurally or in their branching pattern from intrapulmonary arteries connected to central pulmonary arteries. Thus the term collateral artery refers only to the vessel connecting the aorta with the pulmonary segment.

Survival depends on the continued patency of the collateral arteries. In a large collateral some narrowing is desirable to reduce the systemic arterial pressure to a level more appropriate to the pulmonary circulation, but the degree of stenosis is critical because lung growth depends on the

cross-sectional area of the collateral being adequate. Stenoses are seen radiologically and at necropsy, either as a localised constriction where the collateral arises from the aorta or where it anastomoses with a pulmonary artery, or as a narrowed segment. One collateral artery may be stenosed at several points.

Wall structure was examined in 13 collateral arteries, taken from seven published cases of pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries.¹ The purpose of the present study was to assess the probability of collateral arteries remaining patent and growing as the child grows, the possibility of collateral arteries being able to constrict, and how their wall structure compared with that of systemic arteries and the ductus arteriosus. In addition, the structure of the collateral and large intrapulmonary arteries was considered in relation to the most suitable site for insertion of an aortopulmonary anastomosis or a right ventricular conduit.

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Materials and methods

Collateral arterial structure was studied microscopically in 13 arteries taken at random from seven cases of pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries. Serial reconstructions were made of two collaterals from the aorta to the intrapulmonary vessels, and the other collaterals were examined by taking sections at intervals along the same course (Table). The collaterals were always cut in transverse section, with the exception of one serial study in which a very tortuous artery was occasionally cut in longitudinal section. The sections were stained with Miller's elastic van Gieson stain and with a haematoxylin and eosin stain, except for the serial sections, all of which were stained with Miller's elastic van Gieson stain.

Emphasis was given to the following features: (1) the sequence of change in wall structure between the aorta and the lung, (2) the amount and distribution of elastic tissue and smooth muscle cells in the vessel wall, (3) intimal proliferation or cushions, and (4) splitting and fragmentation of the internal and external elastic laminae.

Results

Seven of the 13 collateral vessels arose from the aorta as relatively thin-walled elastic arteries with

a large lumen (Table, Fig. 1). The remaining six collaterals were constricted, being thick-walled and muscular near their origin. All the collaterals save two had a predominantly muscular arterial wall structure throughout most of their course between aorta and lung, the remaining two vessels having a musculoelastic structure (Table). At the hilum of the lung 12 of the 13 collaterals connected with a segmental intrapulmonary artery and provided the only source of blood supply to those segments. As such a collateral artery approached a segmental bronchus it dilated and the wall became elastic in structure (Fig. 1). The remaining collateral anastomosed with a lower lobe branch of a centrally connected pulmonary artery which supplied an entire lung (Fig. 1). This collateral was thick-walled at the hilum and anastomosed with a thick-walled pulmonary artery.

Microscopically, the structure varied in each collateral artery along its course and in different collaterals, as shown by findings in two serial reconstructions.

SERIAL RECONSTRUCTION—CASE A

This collateral was not constricted at its origin from the aorta and the vessel wall was composed largely of long, unbroken elastic fibres (Fig. 2a). Gradually the elastic fibres became thinner and were separated by smooth muscle cells which occupied a progressively greater proportion of the

Table *Material, technique of examination, and summary of results*

Case	Age	No. of collaterals	Technique of examination	Aortic origin	Muscular mid-portion	Collateral PA junction	Intra-pulmonary arterial structure
A	12 days	1	Serial sections	Not narrowed	IP	IC	Normal
B	6 weeks	4	Step sections	Not narrowed	—	IC	Normal
			Step sections	Not narrowed	IP	?	Normal
			Step sections	Not narrowed	IP	?	Normal
			Step sections	Not narrowed	IP	?	Normal
C	3 months	2	Step sections	Narrowed	IP+	IC++	Normal
			Step sections	Narrowed	IP+++ IC	IC+++	Normal
D	4 months	1	Step sections	Narrowed	IP+++ IC Lumen obliterated	?	Normal
E	5 months	1	Serial sections	Not narrowed	IP+	IC	Normal
F	7 months	2	Step sections	Narrowed	IP+++	IC	Normal
			Step sections	Narrowed	IP++ IC	IC	Normal
G	3 years	2	Step sections	Narrowed	Musculoelastic IP	IC+++	Normal
			Step sections	Not narrowed	Musculoelastic IP IC	?	?

IP, intimal proliferation; IC, intimal cushion; ?, indicates structure not examined; PA, pulmonary artery; +, indicates size.

vessel wall as the collateral proceeded towards the lung. The subendothelial elastic fibres condensed into an internal elastic lamina, and short fine fragmented fibres lay in the intima. The external elastic lamina did not entirely surround the circumference of the vessel. The majority of elastic fibres merged into the adventitia. Thus, as the elastic lamellae disappeared a distinct media was formed and the elastic became a muscular artery. The external diameter decreased, and relative wall thickness increased.

In the distal half of the collateral eccentric areas of intimal proliferation were superimposed on an expanded media (Fig. 2b). In this region relative wall thickness increased to 23.4 per cent. Intimal proliferation did not entirely surround the lumen of the collateral at any point along its length and decreased as the collateral approached the hilum of the lung. Nearing the hilum, the proportion of elastic to muscular tissue increased and the vessel dilated. At this point approximately one-fifth of its circumference was covered by an intimal cushion which did not significantly narrow the lumen. Within the lung no intimal cushions were

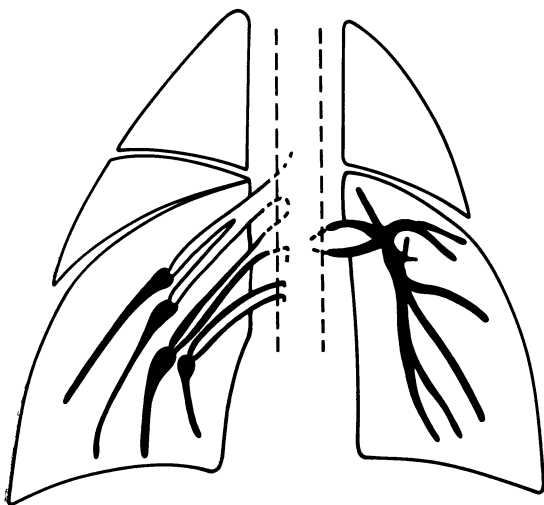


Fig. 1 Diagram to illustrate the possible variation in collateral arterial structure showing, in the right lower lobe from above downwards, a branching collateral artery with a relatively large lumen, a collateral with a wide origin but thick muscular wall distally with intimal proliferation, and a collateral stenosed at its origin from the aorta. In the left lung a large collateral anastomosis with the lower lobe pulmonary artery. Solid lines indicate intrapulmonary arteries, the solid outlines indicate muscular walled collateral arteries, and the interrupted lines indicate the elastic portion of a collateral artery and the aorta.

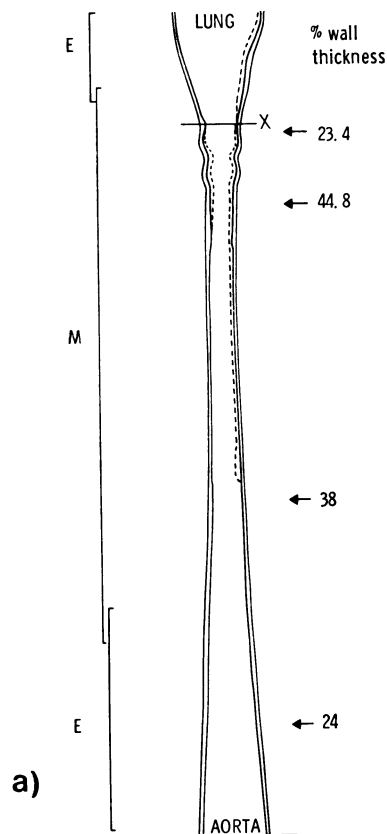
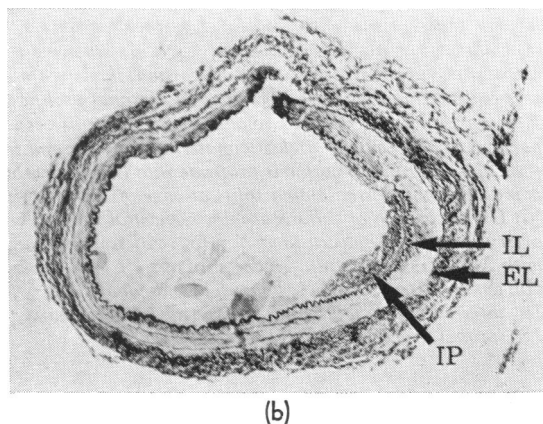


Fig. 2 (a) Scale drawing of serial reconstruction—case A (magnification $\times 10$) showing the reduction in external diameter in the muscular portion of the collateral which is exaggerated where intimal proliferation (-----) is most pronounced. X = plane of section of Fig. 2b. Abbreviations: E, elastic wall; M, muscular wall. (b) Transverse section of collateral artery, showing a muscular wall structure and an area of intimal proliferation (magnification $\times 45$). Abbreviations: IL, internal elastic lamina; EL, external elastic lamina; IP, intimal proliferation.



seen and the vessel had a structure of a normally connected pulmonary artery.

SERIAL RECONSTRUCTION—CASE E

The structural features of this collateral are illustrated in Fig. 3. Intimal cushions were found at each branching point, becoming smaller with each successive division (Fig. 3c and d).

The small collateral destined to join the upper lobar pulmonary artery had a thick media with internal and external elastic laminae. Intimal proliferation covered approximately half the circumference and consisted of an inner layer of fine elastic fibres and an adluminal layer of relatively acellular amorphous material (Fig. 3d). The large parent collateral artery divided again. One vessel remained thick-walled, and in the other intimal cushions developed and beyond this the arterial wall became thin, the proportion of elastic fibres increasing in relation to the amount of smooth muscle.

At this point the vessel became a segmental pulmonary artery of the left lower lobe (Fig. 3d).

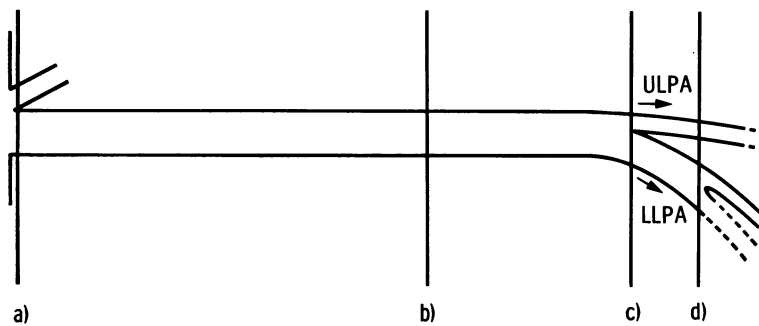
ADDITIONAL FEATURES PRESENT IN THESE AND OTHER COLLATERAL ARTERIES

(1) Aortic origin

Six collateral arteries were narrowed at their aortic origin. At this point, all showed an extremely thick muscular media from which fleshy tongues of muscle encroached on the lumen (Fig. 4). Thick bundles of longitudinal muscle cells lay in the outer half of the media and circumferentially and obliquely orientated muscle cells lay beneath a reduplicated internal elastic lamina.

(2) Mid section

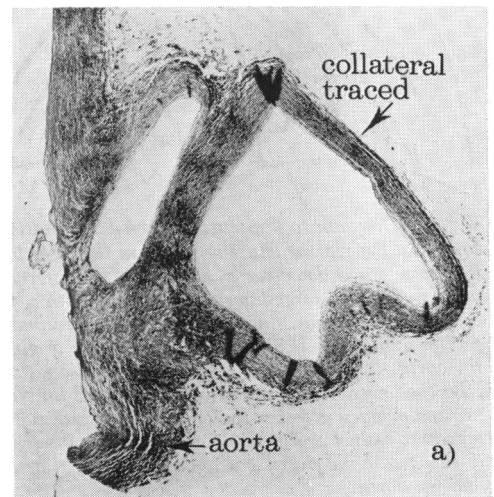
In the mid section of all save two collaterals the arterial wall changed from an elastic to a muscular structure approximately 1.5 to 2 cm from the aorta. External diameter decreased and relative wall

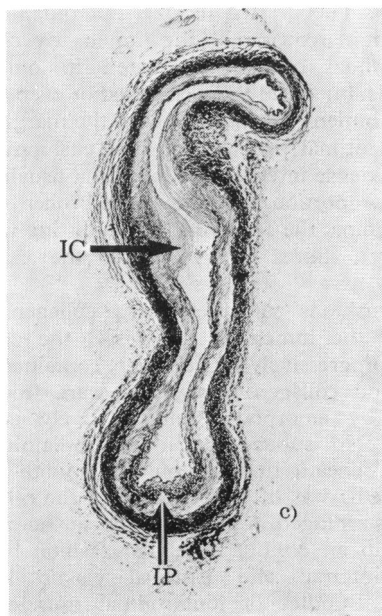
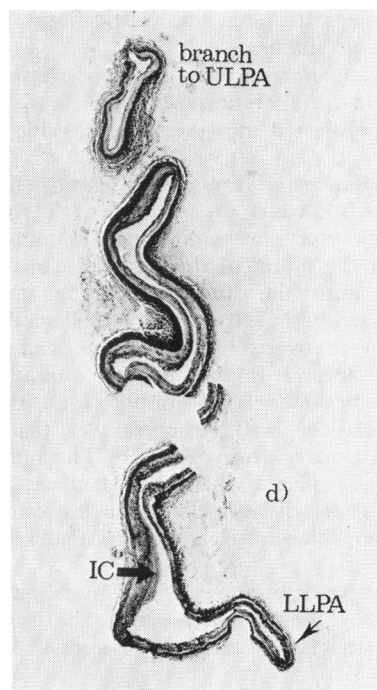
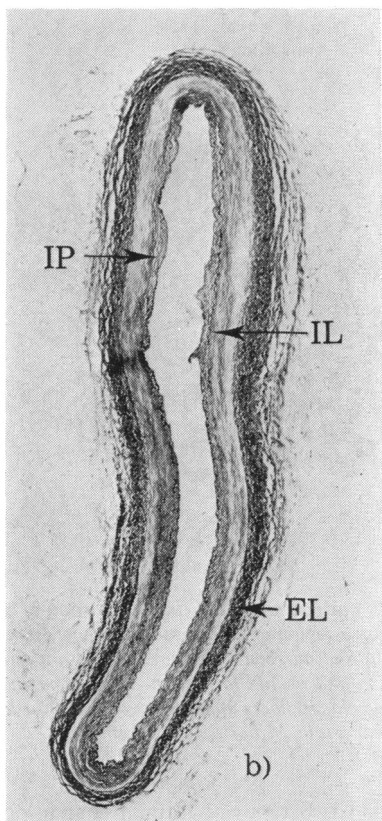


Length after fixation = 1.8 cm

Fig. 3 Serial reconstruction—case E. Line drawing of a collateral artery, from the aorta to where its branches join segmental intrapulmonary arteries. Photomicrographs (a)–(d) are sections taken at the points indicated on the diagram.

(a) collateral arising from the aorta ($\times 13.4$), showing its elastic structure. (b) Muscular mid portion, showing thick media between internal and elastic laminae and intimal proliferation. Note variation in structure around circumference of vessel, particularly in amount of elastic material in media and intima ($\times 28$). (c) Intimal cushions protrude into lumen at a branching point. Internal elastic lamina splits at edge of cushions ($\times 28$). (d) Lowest branch of collateral joins segmental intrapulmonary artery, beyond intimal cushions ($\times 13$). All sections stained with Miller's elastic stain. Abbreviations: ULPA, upper lobe pulmonary artery; LLPA, lower lobe pulmonary artery; IL, internal elastic lamina; EL, external elastic lamina; IP, intimal proliferation; IC, intimal cushion.





thickness increased (Fig. 2, 3, 5, and 6), causing segmental narrowing in all instances, sometimes of a severe degree (Fig. 5 and 6).

The remaining two collateral arteries (case G) had a large lumen. Both had a musculoelastic wall structure. A broken external elastic lamina and a broken, frequently splitting internal elastic lamina bounded a media composed of smooth muscle cells

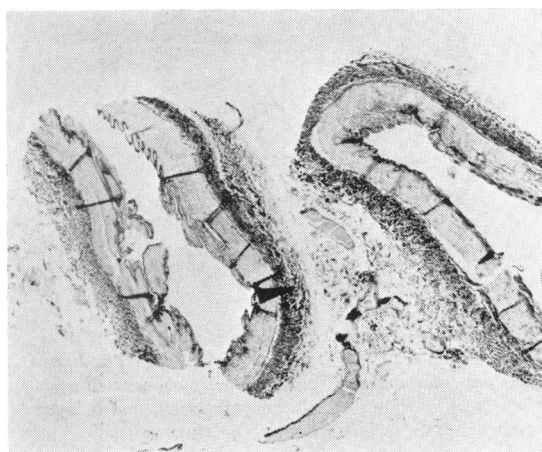


Fig. 4 Transverse sections of a collateral narrowed at its aortic origin, showing a thick media, extensions of which project into the lumen (Miller's elastic stain $\times 29$).

interspersed with long, fine elastic fibres, forming 4 to 8 elastic laminae.

All the collateral arteries save one showed areas of intimal proliferation and, in four, intimal cushions projected into the lumen (Table).

(3) Collateral-pulmonary artery anastomosis

In all vessels in which the structure of the collateral-pulmonary artery anastomosis was examined, near or within the hilum of the lung intimal cushions projected into the lumen, reducing its cross-sectional area (Fig. 3d). In three collaterals, large cushions were covered by a thick layer of amorphous material. Beyond this point the muscular wall gradually became elastic, until within the lung parenchyma the wall structure was that of an elastic pulmonary artery (Fig. 7). The pulmonary arteries were dilated where they connected with a collateral artery, occasionally producing a sinusoidal cavity from which arose abnormally small segmental arteries.

Irrespective of the severity of luminal narrowing produced by the intimal mounds, the distal pulmonary arteries were invariably patent.

STRUCTURE OF INTIMAL CUSHIONS

The type of intimal change varied along the course of each collateral and also in the same region of different collaterals. In the muscular

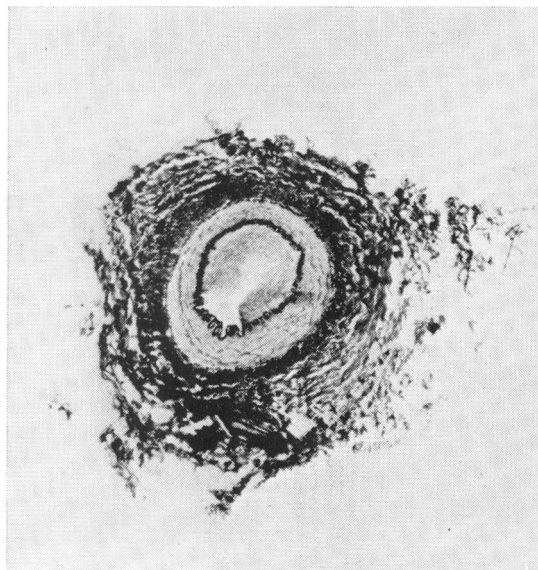


Fig. 6 Transverse section of the mid portion of a collateral at a region of segmental narrowing, showing a thick media and narrowing of the lumen by intimal proliferation and mound formation. Intimal mounds contain fine elastic fibres and are covered with a layer of acellular material (Miller's elastic stain $\times 38$).

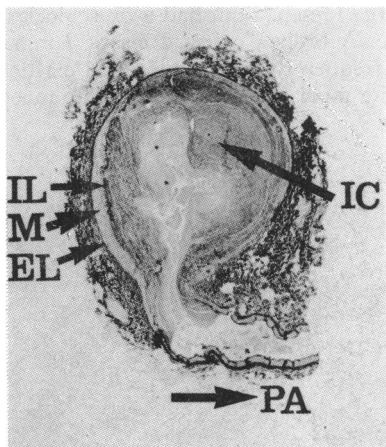


Fig. 5 Transverse section of the mid portion of a collateral at a region of segmental narrowing. The lumen of this muscular artery is almost totally obliterated by intimal proliferation and cushion formation, and a layer of amorphous material containing no elastic tissue (Miller's elastic stain $\times 17$).

Abbreviations: IL, internal elastic lamina; EL, external elastic lamina; M, media; IC, intimal cushion; PA, pulmonary artery.

mid-section two types of intimal change occurred, either small areas of intimal proliferation or large intimal cushions. Small areas of proliferation were present in nearly all cases, even at 12 days of age (Fig. 2b). They varied in size, but did not cause significant narrowing of the lumen. By contrast, large intimal cushions occurred in only four collaterals, but in all they narrowed or even obliterated the lumen (Fig. 5 and 6). At the margin of all areas of intimal proliferation and cushion formation, the dense internal elastic lamina usually split, a larger proportion continuing as a broken internal elastic lamina, the adluminal part splitting into fine fragmented fibres lying within the expanded intima.

The cushions contained many collagen fibres. Towards the lumen of the vessel the cushions became progressively less cellular, contained fewer elastin and collagen fibres, and were frequently covered by amorphous and relatively acellular material. No subendothelial elastic lamina was present. Beneath the cushion the smooth muscle of the media was often thinned and the cells were no longer arranged in a regular concentric manner, but ran in an oblique, irregular fashion between broken internal and external elastic laminae (Fig. 5). Bundles of longitudinal muscle fibres

frequently lay on either side of the internal elastic lamina. The number of elastic fibres usually increased considerably in relation to the amount of smooth muscle.

In three of the four collateral arteries containing large cushions the outer third of the media showed hyaline change, and at this point the lumen was entirely surrounded by intimal proliferation and cushion formation.

At the branching point of a collateral artery the intimal cushions were more clearly defined structures than those described above (Fig. 3c). They consisted of long thin branching elastic fibres, generally running circumferentially around the lumen. They did not have a thick subendothelial elastic lamina, and were not covered by layers of amorphous material. The intimal cushions present at the junction of a collateral and a segmental pulmonary artery were smaller than those found at the branching points, but had a similar discrete appearance (Fig. 3d). In this position, occasionally a thick layer of intimal proliferation, sometimes with a layer of amorphous material, was superimposed on a well-defined intimal cushion.

Discussion

Findings in the present study help to explain the radiological appearances of the collateral arteries during life. As they arose from the aorta some vessels generally had an elastic wall structure and a wide lumen, but others were constricted at their origin because of a thick muscle wall. The external and lumen diameter of the collaterals

narrowed as the elastic vessels came to resemble muscular systemic arteries. Four vessels contained an extremely narrow segment composed of a thick muscle wall with intimal proliferation and cushion formation. At the anastomosis of a collateral with a pulmonary artery intimal cushions were seen in all the collaterals examined, but the extent to which these structures reduced the lumen diameter varied. Distally the pulmonary artery was large, irrespective of the severity of stenosis, and sometimes showed post-stenotic dilatation.

In pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries, survival depends on the collateral arteries. Intimal proliferation and cushion formation was found in the majority of collaterals examined and in several the lumen was almost or totally occluded. Not all the intimal change, however, was necessarily pathological. The small areas of intimal proliferation found in the muscular mid-section of the collaterals were structurally similar to those described by Robertson² in the brachial, popliteal, and coronary arteries of the fetus and by Dock,³ in the coronary arteries of the newborn. Robertson^{2,4} did not regard these fetal cushions as pathological. The normal development of intimal pads in systemic arteries might explain their presence in the collateral arteries of young infants. In systemic arteries, the function of intimal pads is not understood, but they may represent growing points and might also strengthen the vessel wall. Pulsatile stress is thought to stimulate cushion formation, stimulating longitudinal orientation of medial muscle and the formation of muscle in the intima.^{2,4} Collateral arteries are, of course, subject to the pulsatile stress of the thoracic aorta.

As in the present study, intimal cushions or pads have been described at the branching points of brachial, popliteal, and cerebral arteries in the fetus and are thought to have a supportive function.^{2,4,5} They have not been described in the fetal and newborn lung (A Hislop, 1980, personal communication), but in the adult they are present at the mouths of lateral branches arising from the segmental axial artery.⁶

Intimal cushions were also present at the site of anastomosis between a collateral and intrapulmonary artery, the site at which these vessels are probably normally connected in early fetal life and then, presumably, in the normal fetus, are later disconnected when the intrapulmonary arteries become exclusively connected to the sixth arch. In this position, the intimal cushions were frequently covered by a thick layer of intimal proliferation and a superficial relatively structureless layer. This appearance suggests that super-

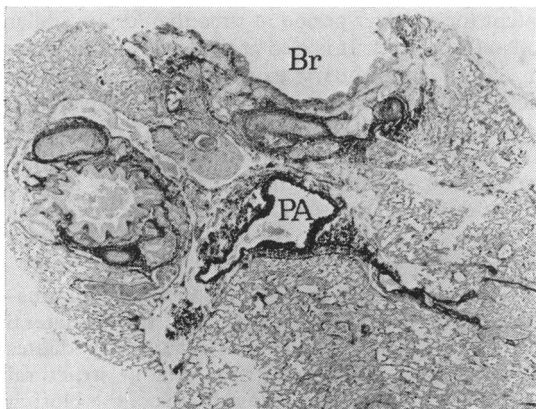


Fig. 7 Cross-section of lung showing an intrapulmonary artery which was connected proximally to a collateral artery. The vessel has the elastic wall structure of a typical pulmonary artery (Miller's elastic stain $\times 21$). Abbreviations: Br, bronchus; PA, pulmonary artery.

imposed on discrete intimal cushions, layers of intimal proliferation caused progressive narrowing of the vessel lumen.

It may be that intimal pads develop *in utero* in collateral and in normal arteries, and in both are the site of early obliterative change.^{3,4} The intimal cushions present in the muscular mid-section of several collaterals were larger than those previously discussed and less discrete. In some collaterals remnants of intimal cushions could be seen beneath a less structured layer of intimal proliferation containing relatively little elastic material. The basic structure of collateral arteries may predispose them to obliterative change. The collateral arteries described in the present study had a thick muscular wall, whereas large conducting arteries so close to the thoracic aorta normally have a predominantly elastic wall structure. The muscular collateral arteries are presumably less distensible and are also capable of contracting in response to a high distending pressure. When the lumen is narrowed the velocity of flow increases, increasing the shearing stress on the endothelium and the likelihood of producing intimal damage and proliferative change.⁷

The structure of the narrowed collateral arteries resembled that of a normally closing ductus arteriosus.⁸ Like the ductus, the collaterals resembled muscular systemic arteries and several contained intimal cushions structurally similar to ductal cushions. Like the normally closing ductus arteriosus, no subendothelial elastic lamina was present. In both collateral arteries and the ductus arteriosus areas of cytolytic necrosis and mucoid lakes occurred in the inner media and base of the intimal cushions. These similarities may indicate only that the structural mechanism by which these muscular arteries, or indeed any muscular artery, are obliterated is similar, irrespective of the functional stimulus which provokes the change. Alternatively, the structural similarities between the narrowed collateral arteries and closing ductus arteriosus and the propensity for both channels to close in early postnatal life may imply that both structures are persistent fetal channels which are destined to close. Boyden⁹ suggested that collateral arteries are persistent segmental arteries which normally close about 50 days after ovulation. We might therefore be witnessing delayed "normal" closure of segmental arteries in infants with pulmonary atresia and ventricular septal defect. This could explain why severe obliterative change was found in such young infants. A high transmural pressure alone might not be sufficient to produce such severe obliterative change so rapidly.

Clearly, not all collateral arteries become severely narrowed because some children with pulmonary atresia, ventricular septal defect, and major aorto-pulmonary collateral arteries reach adolescence. There is evidence to suggest that the variable natural history might be a result of a basic structural difference in the collateral arteries. In the present study two thin-walled collateral arteries present in the 3-year-old child contained a greater amount of elastic tissue than did the collaterals of the younger cases. Two large collateral arteries in a 7-year-old child, not included in the present series, had a wall composed of densely packed elastic laminae. In these four collaterals, intimal change was less frequent and less severe than in the muscular collateral arteries and though the mid-section of one collateral contained a large intimal cushion this did not produce significant narrowing of the wide lumen.

The difference between the wall structure of collaterals with a relatively large lumen found in older children and that in the majority of collateral arteries in the infant group is similar to that between the persistently patent and normally closing ductus arteriosus. A persistent ductus arteriosus usually contains more elastic tissue than a normally closing ductus, sometimes showing lamella formation.⁸ A patent ductus is, however, characterised by a wavy unfragmented subendothelial elastic lamina which continues as a thick fibre on top of the cushions, while in the collateral arteries this elastic lamina became fragmented within the cushions.

These observations suggest that collateral arteries containing a greater proportion of elastic rather than smooth muscle tissue are larger and remain patent for a longer period of time than do muscular collateral arteries. It is also possible that an increase in elastin is secondary to prolonged patency. In the ductus arteriosus, however, there was no relation between age and the occurrence of a subendothelial lamina and the amount of elastic material in the ductus wall.⁸ Further studies of collateral arterial structure in older patients are obviously necessary.

CLINICAL IMPLICATIONS

The question arises as to whether any pharmacological agent might encourage the collateral arteries to remain patent. Prostaglandin E₁ dilates the normally closing ductus, but a structural similarity between the closing ductus and a closing collateral artery does not necessarily imply a functional similarity. Moreover, to be effective prostaglandins would have to be given prophylactically from birth since once fibrous obliterative change is present and the media is thinned the

vessel is unlikely to respond to any vasodilator drug.

A necropsy study obviously gives a biased impression of the natural history of any condition. Findings in the present study, however, indicate that in young infants with pulmonary atresia, ventricular septal defect, and major aortopulmonary collateral arteries, the collateral arteries can undergo obliterative change, and are unlikely to increase in size as the child grows. These observations help explain why infants with this anomaly frequently become increasingly cyanosed during the first months of life. Furthermore, quantitative morphometric analysis of areas of lung periphery perfused by the collateral arteries described in the present series, showed impaired lung growth, usually because of hypoperfusion.¹ Because large occlusive intimal cushions can develop at the junction of collateral and intrapulmonary arteries, an aortopulmonary anastomosis or a right ventricular conduit should be inserted beyond the collateral artery, at the origin of the intrapulmonary vessel.

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